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### (54) Substituted indazole derivatives

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## Description

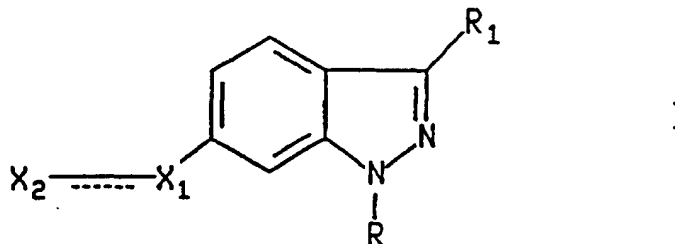
[0001] This invention relates to novel indazole analogs that are selective inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF), and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, and other inflammatory diseases, central nervous system disorders such as depression and multi-infarct dementia, AIDS, septic shock and other diseases involving the production of TNF. This invention also relates to a method of using such compounds in the treatment of the foregoing diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

[0002] Since the recognition that cyclic adenosine phosphate (AMP) is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, *Pharmacol. Rev.*, 12, 265, (1960)), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo *et al.*, *Trends in Pharm. Sci. (TIPS)*, 11, 150, (1990)), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, M. S. Hahid, *TIPS*, 12, 19, (1991)). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M. W. Verghese *et al.*, *J. Mol. Cell Cardiol.*, 12 (Suppl. II), S 61, (1989)) and airway smooth muscle relaxation (T.J. Torphy in "Directions for New Anti-Asthma Drugs," eds S.R. O'Donnell and C. G. A. Persson, 1988, 37 Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects. It has also been disclosed that PDE IV inhibitors are useful in the treatment of diabetes insipidus (*Kidney Int.* 37:362, 1990; *Kidney Int.* 35:494) and central nervous system disorders such as depression and multi-infarct dementia (PCT international application WO 87/06576 (published November 5, 1987)).

[0003] TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, *Fed. of Euro. Bio. Soc. (FEBS) Letters*, 285, 199, (1991)). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C. E. Spooner *et al.*, *Clinical Immunology and Immunopathology*, 62, S11, (1992)).

## Summary of the Invention

[0004] The present invention relates to compounds of the formula I



and to pharmaceutically acceptable salts thereof, wherein:

the broken line indicates a single or double bond;

X<sub>1</sub> is -CR<sub>2</sub>R<sub>3</sub> where said broken line indicates a single bond or -CR<sub>3</sub> where said broken line indicates a double bond;

X<sub>2</sub> is -CR<sub>5</sub>R<sub>7</sub>R<sub>8</sub> where said broken line indicates a single bond or -CR<sub>7</sub>R<sub>8</sub> where said broken line indicates a double bond;

R is -(CH<sub>2</sub>)<sub>m</sub>(C<sub>3</sub>-C<sub>7</sub> cycloalkyl) wherein m is 0 to 2, or C<sub>6</sub>-C<sub>10</sub> aryl;

R<sub>1</sub> is C<sub>1</sub>-C<sub>7</sub> alkyl,

R<sub>2</sub> is H, hydroxy, halo or -OR<sub>9</sub>;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>n</sub>(C<sub>6</sub>-C<sub>10</sub> aryl) or -(CH<sub>2</sub>)<sub>n</sub>(5-10 membered heteroaryl), wherein n is 0 to 3 and R<sub>3</sub> is optionally substituted by 1 to 3 R<sub>4</sub> groups;

each R<sub>4</sub> is independently selected from halo, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl or -OR<sub>5</sub>,

each R<sub>5</sub> is independently H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>7</sub> is R<sub>3</sub>,

R<sub>8</sub> is R<sub>5</sub>, and

R<sub>9</sub> is formyl, carbamoyl, thiocarbamyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, (C<sub>1</sub>-C<sub>4</sub> alkoxy)C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkanoyl,

wherein the alkyl moieties of said  $R_9$  groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, and  $C_1$ - $C_4$  alkoxy.

[0005] Preferred compounds of formula I include those wherein  $R_1$  is ethyl and R is cyclopentyl, cyclohexyl, or  $C_6$ - $C_{10}$  aryl.

[0006] Other preferred compounds of formula I include those wherein  $R_3$  is  $-(CH_2)_n(C_6-C_{10}$  aryl) or  $-(CH_2)_n(5-10$  membered heteroaryl), wherein n is 0 to 3, and, more preferably, wherein  $R_3$  is phenyl or pyridin-4-yl.

[0007] Other preferred compounds of formula I include those wherein  $R_7$  is  $-(CH_2)_n(5-10$  membered heteroaryl), wherein n is 0 to 3, and, more preferably, wherein  $R_7$  is pyridin-4-yl.

[0008] Specific embodiments of the compounds of formula I include those wherein the broken line indicates a single bond,  $R_2$  is H,  $R_3$  is phenyl, 3-methyl-phenyl, 4-pyridyl, 2-furyl, 2-thienyl, or 2-methoxy-phenyl,  $R_5$  is H,  $R_8$  is H, and  $R_7$  is 4-pyridyl, 3-methyl-4-imidazolyl, 3,5-dichloro-4-pyridyl, or 4-pyrimidinyl.

[0009] Other specific embodiments of the compounds of formula I include those wherein the broken line indicates a double bond,  $R_3$  is phenyl, 4-methoxy-phenyl, 2-furyl, 2-thienyl, 4-fluoro-phenyl, 4-trifluoromethyl-phenyl or 2-methoxy-phenyl,  $R_8$  is H, and  $R_7$  is 4-pyridyl.

[0010] Specific preferred compounds include the following:

1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;  
1-cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole;  
1-cyclopentyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazole;  
1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;  
1-cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole;  
1-cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazole;

and pharmaceutically acceptable salts of the foregoing compounds.

[0011] Other specific preferred compounds include the following:

1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;  
1-cyclohexyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole;  
1-cyclohexyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazole;  
1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;  
1-cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole;  
1-cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazole;

and pharmaceutically acceptable salts of the foregoing compounds.

[0012] The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) comprising a therapeutically effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0013] The present invention further relates to the preparation of medicaments for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal, such as a human, comprising a therapeutically effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt thereof.

[0014] The present invention further relates to a pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, diabetes insipidus, autoimmune diabetes, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, dermatitis, depression or multi-infarct dementia, comprising a therapeutically effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt, thereof together with a pharmaceutically acceptable carrier.

[0015] This invention further relates to the preparation of medicaments for treating or preventing the foregoing specific diseases and conditions in a mammal, such as a human, comprising a therapeutically effective amount of a compound

according to formula I, as defined above, or a pharmaceutically acceptable salt thereof.

[0016] The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

5 [0017] The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties.

[0018] The term "alkoxy", as used herein, unless otherwise indicated, includes -O-alkyl groups wherein alkyl is as defined above.

[0019] The term "alkanoyl", as used herein, unless otherwise indicated, includes -C(O)-alkyl groups wherein alkyl is as defined above.

10 [0020] The term "cycloalkyl", as used herein, unless otherwise indicated, includes saturated monovalent cyclo hydrocarbon radicals including cyclobutyl, cyclopentyl and cycloheptyl.

[0021] The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

15 [0022] The term "heterocyclyl", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with an oxo moiety. An example of a 5-membered heterocyclic group is thiazolyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include benzimidazolyl.

20 [0023] The term "heteroaryl", as used herein, unless otherwise indicated, includes aromatic heterocyclic groups wherein heterocyclic is as defined above.

[0024] The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula I.

25 [0025] Certain compounds of formula I may have asymmetric centers and therefore exist in different enantiomeric forms, and certain compounds of formula I may exist as cis and trans isomers. This invention relates to the use of all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

### 30 Detailed Description of the Invention

[0026] The following reaction schemes 1-3 illustrate the preparation of the compounds of the present invention. Unless otherwise indicated, R, R<sub>1</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>7</sub> and R<sub>8</sub> in the reaction schemes are as defined above.

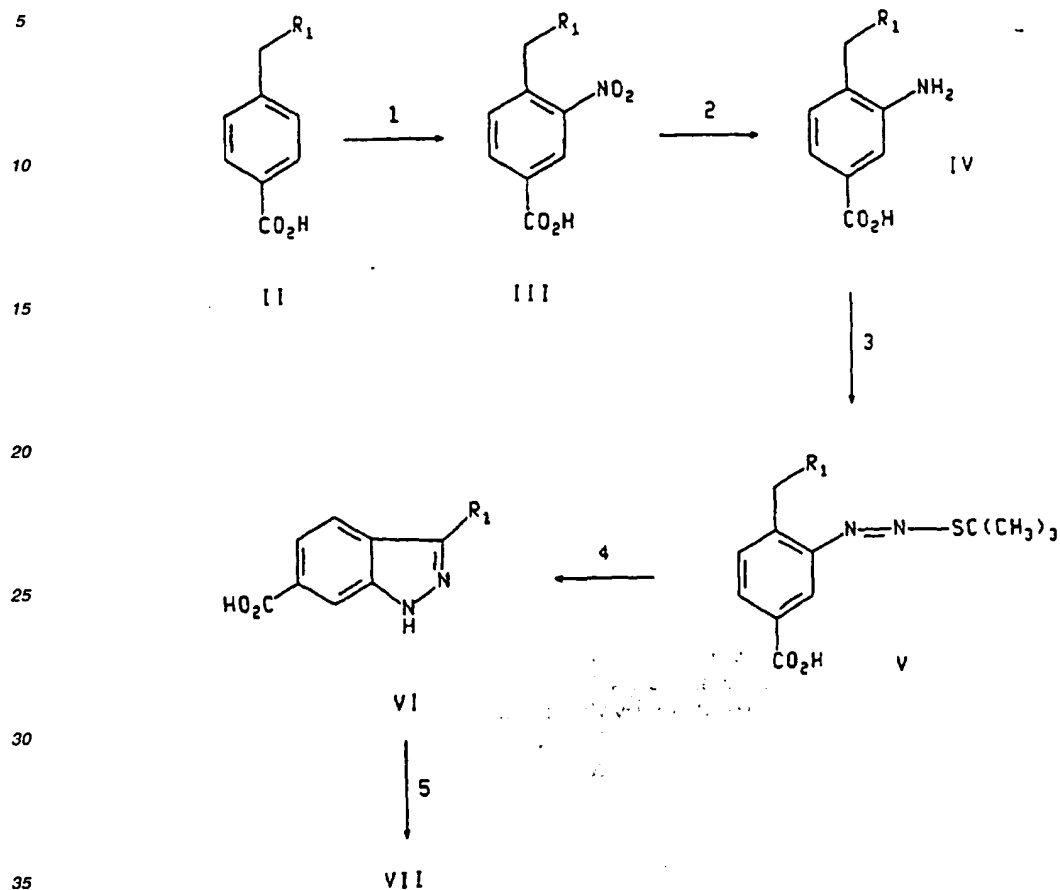
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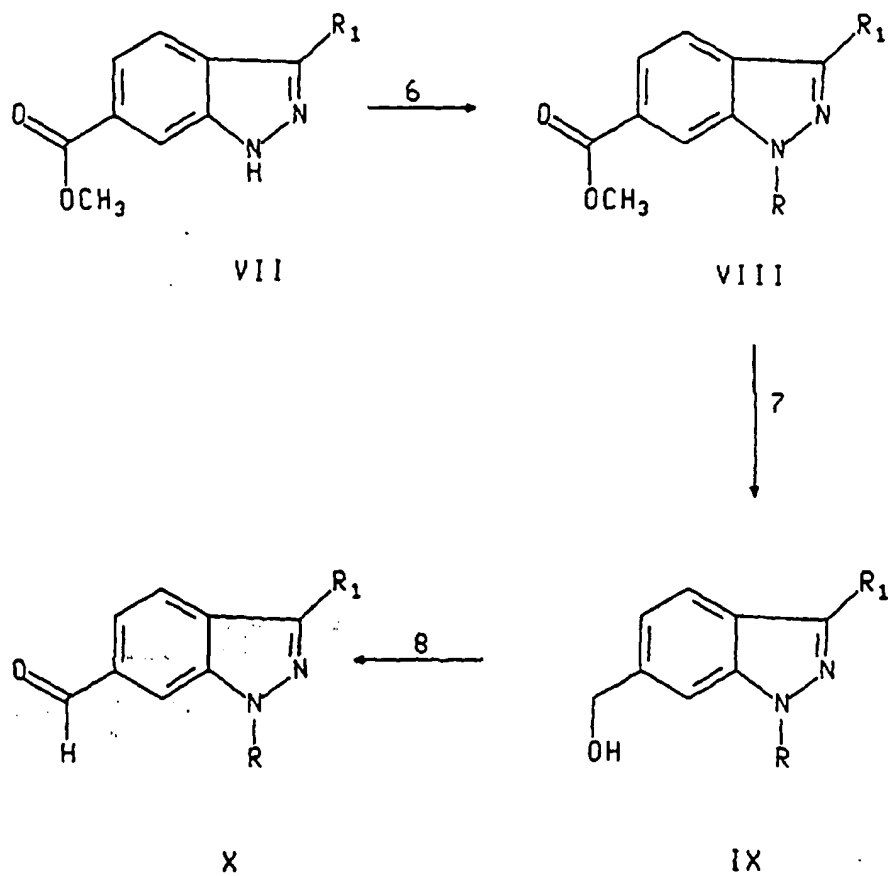
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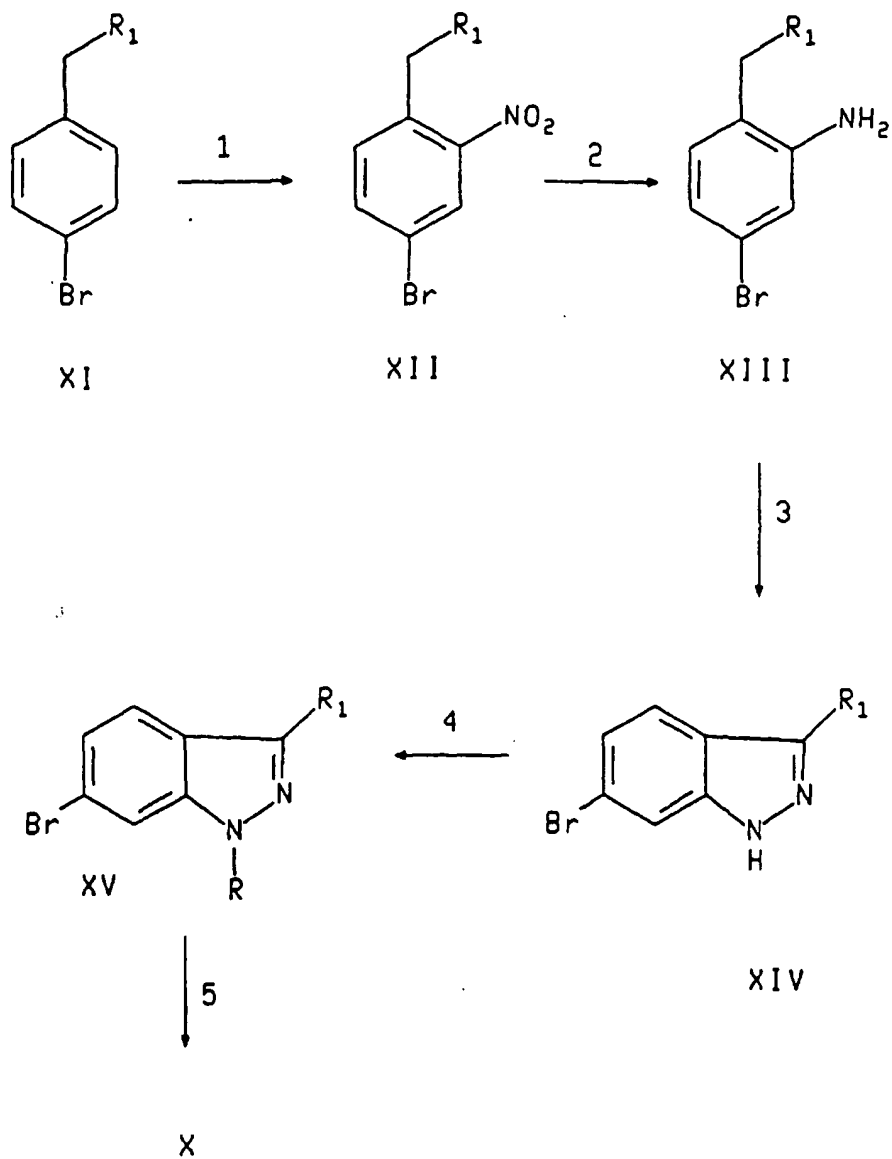
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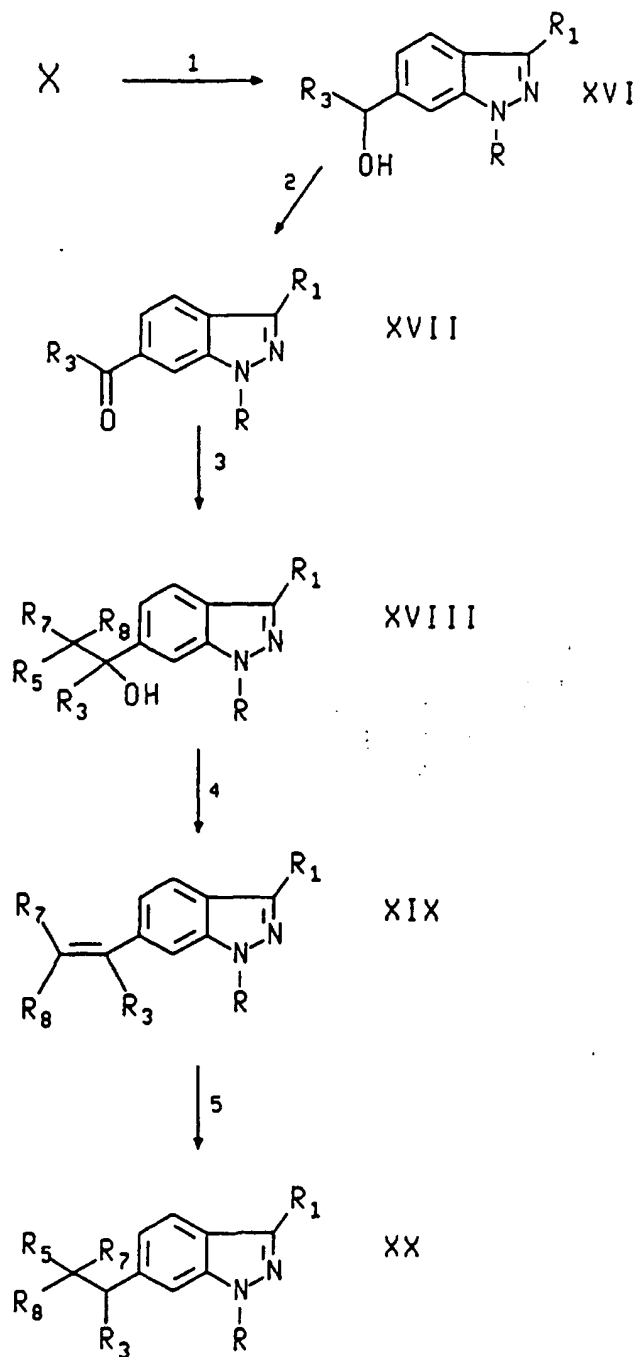
Scheme 1

Scheme 1 continued



Scheme 2



Scheme 3

[0027] The preparation of compounds of formula I can be carried out by one skilled in the art according to one or more of the synthetic methods outlined in Schemes 1-3 above and the examples referred to below. In step 1 of Scheme 1, the carboxylic acid of formula II, which is available from known commercial sources or can be prepared according to methods known to those skilled in the art, is nitrated under standard conditions of nitration ( $\text{HNO}_3/\text{H}_2\text{SO}_4$ ,  $0^\circ\text{C}$ ) and



the resulting nitro derivative of formula III is hydrogenated in step 2 of Scheme 1 using standard hydrogenation methods ( $H_2$ -Pd/C under pressure) at ambient temperature (20-25°C) for several hours (2-10 hours) to provide the compound of formula IV. In step 3 of scheme 1, the amino benzoic acid of formula IV is reacted with a base such as sodium carbonate under aqueous conditions and gently heated until mostly dissolved. The reaction mixture is chilled to a lower temperature (about 0°C) and treated with sodium nitrate in water. After about 15 minutes, the reaction mixture is slowly transferred to an appropriate container holding crushed ice and a strong acid such as hydrochloric acid. The reaction mixture is stirred for 10-20 minutes and then added, at ambient temperature, to a solution of excess t-butyl thiol in an aprotic solvent such as ethanol. The reaction mixture is acidified to a pH of 4-5 through addition of an inorganic base, preferably saturated aqueous  $Na_2CO_3$ , and the reaction mixture is allowed to stir at ambient temperature for 1-3 hours. Addition of brine to the reaction mixture, followed by filtration, provides the sulfide of formula V.

[0028] In step 4 of Scheme 1, the sulfide of formula V is converted to the corresponding indazole carboxylic acid of formula VI by reacting the sulfide of formula V with a strong base, preferably potassium t-butoxide, in dimethyl sulfoxide (DMSO) at ambient temperature. After stirring for several hours (1-4 hours), the reaction mixture is acidified with a strong acid, such as hydrochloric or sulfuric acid, and then extracted using conventional methods. In step 5 of Scheme 1, the indazole carboxylic acid of formula VI is converted to the corresponding ester of formula VII by conventional methods known to those skilled in the art. In step 6 of Scheme 1, the compound of formula VIII is provided through alkylation of the ester of formula VII by subjecting the ester to conventional alkylation conditions (strong base/various alkylating agents and, optionally, a copper catalyst such as  $CuBr_2$ ) in a polar aprotic solvent, such as tetrahydrofuran (THF), N-methylpyrrolidinone or dimethylformamide (DMF), at ambient or higher temperature (25-200°C) for about 6-24 hrs, preferably about 12 hours. In step 7 of Scheme 1, the compound of formula VIII is converted to the corresponding alcohol of formula IX by following conventional methods known to those skilled in the art for reducing esters to alcohols. Preferably, the reduction is effected through use of a metal hydride reducing agent, such as lithium aluminum hydride, in a polar aprotic solvent at a low temperature (about 0°C). In step 8 of Scheme 1, the alcohol of formula IX is oxidized to the corresponding aldehyde of formula X according to conventional methods known to those skilled in the art. For example, the oxidation can be effected through use of a catalytic amount of tetrapropylammonium perruthenate and excess N-methylmorpholine-N-oxide, as described in J. Chem. Soc., Chem. Commun., 1625 (1987), in an anhydrous solvent, preferably methylene chloride.

[0029] Scheme 2 provides an alternative method of preparing the aldehyde of formula X. In step 1 of Scheme 2, the compound of formula XI is nitrated using conventional nitration conditions (nitric and sulfuric acid) to provide the compound of formula XII. In step 2 of Scheme 2, the nitro derivative of formula XII is reduced to the corresponding amine of formula XIII according to conventional methods known to those skilled in the art. Preferably, the compound of formula XII is reduced to the amine of formula XIII using anhydrous stannous chloride in an anhydrous aprotic solvent such as ethanol. In step 3 of Scheme 2, the amine of formula XIII is converted to the corresponding indazole of formula XIV by preparing the corresponding diazonium tetrafluoroborates as described in A. Roe, *Organic Reactions*, Vol. 5, Wiley, New York, 1949, pp. 198-206, followed by phase transfer catalyzed cyclization as described in R. A. Bartsch and I. W. Yang, J. Het. Chem. 21, 1063 (1984). In step 4 of Scheme 2, alkylation of the compound of formula XIV is performed using standard methods known to those skilled in the art (i.e. strong base, polar aprotic solvent and an alkyl halide) to provide the N-alkylated compound of formula XV. In step 5 of Scheme 2, the compound of formula XV is subjected to metal halogen exchange employing an alkyl lithium, such as n-butyl lithium, in a polar aprotic solvent, such as THF, at low temperature (-50°C to 100°C (-78°C preferred)) followed by quenching with DMF at low temperature and warming to ambient temperature to provide the aldehyde intermediate of formula X.

[0030] Scheme 3 illustrates the preparation of the compounds of formula I. In step 1 of Scheme 3, the intermediate aldehyde of formula X is reacted with a compound of formula  $R_3-Li$ , wherein  $R_3$  is as defined above, in THF at a temperature within the range of about -78°C to ambient temperature (20-25°C) for a period of about 30 minutes to 3 hours to provide the alcohol intermediate of formula XVI. In step 2 of Scheme 3, the intermediate of formula XVI is reacted in the presence of tetrapropylammonium perruthenate (VII) and 4A molecular sieves in N-methylmorpholine N-oxide and methylene chloride at ambient temperature for about 1 hour to provide the ketone intermediate of formula XVII. In an alternative, the ketone intermediate of formula XVII can be synthesized by reacting the intermediate of formula XV with a compound of formula  $R_3-CN$ , wherein  $R_3$  is as defined above, in the presence of n-butyllithium in THF at a temperature of about -78°C for about 45 minutes and then warming the mixture to -10°C for about 30 minutes to provide the intermediate of formula XVII. In step 3 of Scheme 3, the intermediate of formula XVII is reacted with a compound of formula  $CH_2R_5R_7R_8$ , wherein  $R_5$ ,  $R_7$ , and  $R_8$  are as defined above, in the presence of n-butyllithium in THF at a temperature of about -78°C for about 1 hour and then warming the mixture to ambient temperature for about 30 minutes to provide the intermediate of formula XVIII. In step 4 of Scheme 3, the intermediate of formula XVIII is reacted in the presence of p-toluenesulfonic acid and toluene and heated to reflux for about 7 hours to provide the compound of formula XIX which corresponds to the compound of formula I wherein the dashed line indicates a double bond. This reaction proceeds directly where  $R_5$  or  $R_8$  is hydrogen. In step 5 of Scheme 3, the compound of formula XIX is hydrogenated in the presence of palladium on carbon in ethanol and triethylamine under 25 psi  $H_2$  at ambient

temperature for about 3.5 hours followed by separation of the reaction product and dissolution of the reaction product in ether and 1 N hydrochloric acid to provide the compound of formula XX. The compound of formula XX corresponds to the compound of formula I wherein the dashed line indicates a single bond.

**[0031]** The compounds of formula I can also be prepared following one or more synthetic methods that are disclosed in published patent applications. In particular, using the intermediates described in Schemes 1-3, referred to above, in particular the intermediates of formulas VIII, X, and XV, those skilled in the art can prepare the compounds of formula I using analogous synthetic methods that have been described for compounds in which a phenyl ring is substituted for the indazole ring in the compounds of formula I. Such analogous synthetic methods are disclosed in the following published PCT international applications: WO 94/14742 (published July 7, 1994); WO 94/14800 (published July 7, 1994); WO 94/20446 (published September 15, 1994); WO 94/20455 (published September 15, 1994); WO 95/17392 (published June 29, 1995); WO 95/17399 (published June 29, 1995), WO 95/35284, WO 95/35285, and WO 96/00215. The foregoing published PCT international patent applications are incorporated herein by reference in their entirety.

**[0032]** Specifically, the compounds of formula I wherein  $R_3$  and  $R_7$  are independently  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$  and  $R_8$  is H or  $C_1-C_6$  alkyl can be prepared by following analogous synthetic methods disclosed in WO 94/14742 and WO 94/14800, both of which are referred to above. The compounds of formula I wherein  $R_3$  and  $R_7$  are independently H,  $C_1-C_6$  alkyl, cyano, cyanomethyl,  $-CO_2(CH_2)_n(C_6-C_{10} \text{ aryl})$ ,  $-C(Y)NR_5R_6$  or  $-C(Y)NR_5(CH_2)_n(C_6-C_{10} \text{ aryl})$  and  $R_8$  is  $-(CH_2)_p(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_p(C_6-C_{10} \text{ heteroaryl})$  can be prepared by following analogous synthetic methods disclosed in WO 94/20446 and WO 94/20455, both of which are referred to above. The compounds of formula I wherein  $R_3$  is  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , and  $R_7$  is 2-oxo-pyridyl, 3-oxo-pyridyl, 4-oxo-pyridyl, 2-oxo-pyrrolyl, 4-oxo-thiazolyl, 4-oxo-piperidyl, 2-oxo-quinolyl, 4-oxo-quinolyl, 1-oxo-isoquinolyl, 4-oxo-oxazolyl, 5-oxo-pyrazolyl, 5-oxo-isoxazolyl, or 4-oxo-isoxazolyl, can be prepared by following analogous methods disclosed in WO 95/17392, which is referred to above. The compounds of formula I wherein  $R_3$  is  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$  optionally substituted by an  $R_{10}$  substituent, and  $R_7$  is  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , can be prepared by following analogous methods disclosed in WO 95/17399, which is referred to above. The compounds of formula I wherein  $R_3$  is benzyloxy and  $R_7$  is  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , can be prepared by following analogous methods disclosed in WO 95/35284, which is referred to above. The compounds of formula I wherein the dashed line indicates a single bond and  $X_2$  is  $-C(=NOR_{11})R_{12}$  can be prepared by following analogous methods disclosed in WO 96/00215, which is referred to above.

**[0033]** The compounds of formula I can be resolved into separate enantiomers by using a chiral LC technique according to the following conditions: column: Chiralcel<sup>®</sup> OD (250 x 4.6 mm); Mobile phase: 50:50:0.1 (Hexane:2-propanol:diethylamine); Flow rate: 1 mL/minute; detection: UV (230 nm); temperature: ambient (20-25°C); injection volume: 20  $\mu$ L. The compounds of formula I can also be resolved into separate enantiomers according to other techniques familiar to those skilled in the art, including those described in J. March, Advanced Organic Chemistry, (4th Edition, J. Wiley & Sons), 1992, pages 118-125.

**[0034]** The compounds of formula I that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to humans or animals, it is often desirable in practice to initially isolate the compound of formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is readily obtained. The desired acid addition salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid. Pharmaceutically acceptable salts of amino groups include hydrochloride (preferred), hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. Cationic salts of the compounds of formula I are similarly prepared except through reaction of a carboxy group, such as where  $R_6$  is carboxy, with an appropriate cationic salt reagent such as sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine, tromethamine, or diethanolamine.

**[0035]** For administration to humans in the curative or prophylactic treatment of inflammatory diseases, oral dosages of a compound of formula I or a pharmaceutically acceptable salt thereof (the active compounds) are generally in the range of 0.1 to 1000 mg daily, in single or divided doses, for an average adult patient (70 kg). The active compounds can be administered in single or divided doses. Individual tablets or capsules should generally contain from 0.1 to 100 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the

particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

[0036] For administration to humans for the inhibition of TNF, a variety of conventional routes may be used including orally, parenterally, topically, and rectally (suppositories). In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg in single or divided doses. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

[0037] For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substance; for example, enough salts or glucose to make the solution isotonic.

[0038] Additionally, the active compounds may be administered topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

[0039] The therapeutic compounds may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal species and the disease or disorder being treated. The therapeutic compounds may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The therapeutic compounds may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. As an alternative the therapeutic compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

[0040] The ability of the compounds of formula I or the pharmaceutically acceptable salts thereof to inhibit PDE IV may be determined by the following assay.

[0041] Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4 °C. The supernatant is filtered twice through a 0.22 µm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF Buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE<sub>IV</sub> activity determined by [<sup>3</sup>H]cAMP hydrolysis and the ability of a known PDE<sub>IV</sub> inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

[0042] Compounds are dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM and diluted 1:25 in water (400 µM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. The final DMSO concentration in the assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as the final concentrations in the assay tube).

- i) 25 µl compound or DMSO (1%, for control and blank)
- ii) 25 µl pH 7.5 Tris buffer
- iii) [<sup>3</sup>H]cAMP (1 µM)
- iv) 25 µl PDE IV enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

[0043] The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are added to an AFF-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [<sup>3</sup>H]cAMP is washed with 2 x 6 ml washing buffer, and [<sup>3</sup>H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [<sup>3</sup>H].

$$\% \text{ inhibition} = 1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$$

IC<sub>50</sub> is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [<sup>3</sup>H]cAMP to [<sup>3</sup>H]5'AMP. [0044] The ability of the compounds I or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating disease involving the production of TNF is shown by the following *in vitro* assay:

[0045] Peripheral blood (100 mls) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by FICOLL/Hypaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1 x 10<sup>6</sup> cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/step and nystatin). Monocytes are plated as 1 x 10<sup>6</sup> cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10 µl) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10 µl) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C. At the end of the incubation period TNF was analyzed by a sandwich EUSA (R&D Quantikine Kit). IC<sub>50</sub> determinations are made for each compound based on linear regression analysis.

[0046] The following Examples and Preparations illustrate the preparation of the compounds of the present invention.

#### PREPARATION 1

##### 1 -Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

[0047]

A. 3-Nitro-4-propyl-benzoic acid. 9.44 g (57.5 mmol, 1.0 equiv) of 4-propylbenzoic acid were partially dissolved in 50 mL concentrated H<sub>2</sub>SO<sub>4</sub> and chilled in an ice bath. A solution of 4.7 mL (74.7 mmol, 1.3 equiv) concentrated HNO<sub>3</sub> in 10 mL concentrated H<sub>2</sub>SO<sub>4</sub> was added dropwise over 1-2 min. After stirring 1 hour at 0°C, the reaction mixture was poured into a 1 L beaker half full with ice. After stirring 10 min., the white solid that formed was filtered, washed 1 x H<sub>2</sub>O, and dried to give 12.01 g (100%) of the title compound: mp 106-109°C; IR (KBr) 3200-3400, 2966, 2875, 2667, 2554, 1706, 1618, 1537, 1299, 921 cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.90 (t, 3H, J=7.4 Hz), 1.59 (m, 2H), 2.82 (m, 2H), 7.63 (d, 1H, J= 8.0 Hz), 8.12 (dd, 1H, J=1.7, 8.0 Hz), 8.33 (d, 1H, J=1.7 Hz); <sup>13</sup>C NMR (75.5 MHz, DMSO-d<sub>6</sub>) δ 14.2, 23.7, 34.2, 125.4, 130.5, 132.9, 133.6, 141.4, 149.5, 165.9; Anal. calcd for C<sub>10</sub>H<sub>11</sub>NO<sub>4</sub>·1/4H<sub>2</sub>O: C, 56.20; H, 5.42; N, 6.55. Found: C, 56.12; H, 5.31; N, 6.81.

B. 3-Amino-4-propyl-benzoic acid. A mixture of 11.96 g (57.2 mmol) 3-nitro-4-propyl-benzoic acid and 1.5 g 10% Pd/C, 50% water wet, in 250 mL CH<sub>3</sub>OH was placed on a Parr hydrogenation apparatus and shaken under 25 psi H<sub>2</sub> at ambient temperature (20-25° C). After 1 hours, the reaction mixture was filtered through Celite®, and the filtrate concentrated and dried to give 9.80 g (96%) of a pale yellow crystalline solid: mp 139.5-142.5°C; IR (KBr) 3200-2400, 3369, 3298, 2969, 2874, 2588, 1690, 1426, 1260, 916, 864 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.90 (t, 3H, J=7.2 Hz), 1.52 (m, 2H), 2.42 (m, 2H), 5.08 (br s, 2H), 6.96 (d, 1H, J=7.8 Hz), 7.05 (dd, 1H, J=1.7, 7.8 Hz), 7.20 (d, 1H, J=1.7 Hz), MS (CI, NH<sub>3</sub>) m/z 180 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>·1/3H<sub>2</sub>O: C, 64.85; N, 7.89; H, 7.56. Found: C, 64.69; H, 7.49; N, 7.86.

C. 3-Carboxy-6-propyl-benzenediazo t-butyl sulfide. A mixture of 8.80 g (49.1 mmol, 1.0 equiv) 3-amino-4-propyl-benzoic acid and 2.34 g (22.1 mmol, 0.45 equiv) sodium carbonate in 55 mL H<sub>2</sub>O was heated gently with a heat gun until mostly dissolved. The reaction mixture was chilled in an ice bath, and a solution of 3.73 g (54.0 mmol, 1.0 equiv) sodium nitrite in 27 mL H<sub>2</sub>O was added dropwise. After 15 minutes, the reaction mixture was transferred to a dropping funnel and added over 10 minutes to a beaker containing 55 g of crushed ice and 10.6 mL concentrated HCl. After stirring 10 minutes, the contents of the beaker were transferred to a dropping funnel and added over 5 minutes to a room temperature solution of 5.31 mL (47.1 mmol, 0.96 equiv) t-butyl thiol in 130 mL ethanol. The pH was adjusted to 4-5 by addition of saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution, and the reaction mixture was allowed to stir 1 hour at ambient temperature (20-25°C). 200 mL brine were added, and the mixture was filtered. The solid was washed 1 x H<sub>2</sub>O and dried overnight to give 12.25 g (89%) of a brown/rust colored powder (caution-stench): mp 102°C (dec); IR (KBr) 3200-2400, 2962, 2872, 2550, 1678, 1484, 1428, 1298, 1171 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.84 (t, 3H, J=7.3 Hz), 1.48 (m, 2H), 1.55 (s, 9H), 2.42 (m, 2H), 7.29 (d, 1H, J=1.6 Hz), 7.50 (d, 1H, J=8.0 Hz), 7.86 (dd, 1H, J=1.7, 7.9 Hz), 13.18 (br s, 1H); MS (thermospray, NH<sub>4</sub>OAc) m/z 281 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S: C, 59.96; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.32; N, 10.02.

D. 3-Ethyl-1H-indazole-6-carboxylic acid. A solution of 12.0 g (42.8 mmol, 1.0 equiv) 3-carboxy-6-propyl-benzenediazo t-butyl sulfide in 150 mL DMSO was added dropwise over 15 minutes to an ambient temperature solution of 44.6 g (398 mmol, 9.3 equiv) potassium t-butoxide in 200 mL dimethylsulfoxide (DMSO). After stirring 2 hours at ambient temperature, the reaction mixture was poured into 1.5 L of 0°C 1N HCl, stirred 5 minutes, then extracted 2 x 350 mL ethyl acetate. The ethyl acetate extracts (caution - stench) were combined, washed 2 x 250 mL H<sub>2</sub>O, and dried over MgSO<sub>4</sub>. Filtration, concentration of filtrate and drying gave a tan solid, which was triturated with 1

L of 1:3 Et<sub>2</sub>O/Hexanes and dried to give 7.08 g (87%) of a tan crystalline powder: mp 248-251°C; IR (KBr) 3301, 3300-2400, 2973, 2504, 1702, 1455, 1401, 1219 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.31 (t, 3H, J=7.6 Hz), 2.94 (q, 2H, J=7.6 Hz), 7.63 (dd, 1H, J=1.1, 8.4 Hz), 7.81 (d, 1H, J=8.4 Hz), 8.06 (d, 1H, J=1.1 Hz), 12.95 (br s, 1H); MS (CI, NH<sub>3</sub>) m/z 191 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.66; H, 5.42; N, 14.80.

E. 3-Ethyl-1H-indazole-6-carboxylic acid methyl ester. 8.78 g (45.8 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to an ambient temperature solution of 7.92 g (41.6 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid, 16.9 mL (416 mmol, 10 equiv) methanol and 5.59 g (45.8 mmol, 1.1 equiv) dimethylaminopyridine (DMAP) in 250 mL CH<sub>2</sub>Cl<sub>2</sub>. After 18 hours at room temperature, the reaction mixture was concentrated to 150 mL, diluted with 500 mL ethyl acetate, washed 2 x 100 mL 1N HCl, 1 x 100 mL H<sub>2</sub>O, 1 x 100 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 7.8 g of a brown solid, which was purified on a silica gel column (30% to 50% ethyl acetate/hexane gradient) to give 6.41 g (75%) of a tan solid: mp 107-108°C; IR (KBr) 3100-2950, 1723, 1222 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.19 (m, 1H), 7.7-7.8 (m, 2H), 3.96 (s, 3H), 3.05 (q, 2H, J=7.7 Hz), 1.43 (t, 3H, 7.7 Hz); MS (CI, NH<sub>3</sub>) m/z 205 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.88; H, 6.01; N, 13.96.

F. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester. 1.17 g (29.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in one portion to an ambient temperature solution of 5.7 g (27.9 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 125 mL anhydrous DMF. After 20 min., 3.89 mL (36.6 mmol, 1.3 equiv) cyclopentyl bromide were added dropwise, and the reaction mixture allowed to stir overnight at room temperature. The mixture was then poured into 1 L H<sub>2</sub>O and extracted 3 x 450 mL ethyl acetate. The organic extracts were combined, washed 3 x 400 mL H<sub>2</sub>O, 1 x 200 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave an amber oil, which was purified on a silica gel column (10% ethyl acetate/hexanes, gravity) to give 5.48 g (72%) of a clear oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.16 (d, 1H, J=1.0 Hz), 7.7 (m, 2H), 5.00 (quintet, 1H, J=7.5 Hz), 3.97 (s, 3H), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.39 (t, 3H, J=7.6 Hz); HRMS calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 272.1526. Found: 272.15078.

G. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol. 7 mL (7.0 mmol, 1.0 equiv) lithium aluminum hydride, 1.0 M solution in THF, were added to a 0°C solution of 1.02 g (7.05 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 50 mL anhydrous THF. After 20 minutes, 1 mL methanol was added cautiously, then the reaction mixture was poured into 500 mL of 5% H<sub>2</sub>SO<sub>4</sub> and extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 2 x 40 mL H<sub>2</sub>O, 1 x 40 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate, and drying gave 1.58 g of a clear oil, which was purified on a silica gel column to give 1.53 g (89%) clear oil: IR (CHCl<sub>3</sub>) 3606, 3411, 3009, 2972, 2875, 1621, 1490 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.65 (d, 1H, J=8.0 Hz), 7.42 (s, 1H), 7.06 (dd, 1H, J=1.0, 8.2 Hz), 4.92 (quintet, 1H, J=7.7 Hz), 4.84 (s, 2H), 2.98 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 3H), 1.38 (t, 3H, J=7.6 Hz); MS (thermospray, NH<sub>4</sub>OAc) m/z 245 (M+H<sup>+</sup>, base); HRMS calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O + H: 245.1654. Found: 245.1675.

H. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde. 106 mg (0.301 mmol, 0.05 equiv) tetrapropylammonium perruthenate (VII) were added to a room temperature suspension of 1.47 g (6.02 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol, 1.06 g (9.03 mmol, 1.5 equiv) N-methylmorpholine N-oxide and 3.01 g 4A molecular sieves in 12 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub>. After 20 minutes the reaction mixture was filtered through a short column of silica gel (eluted with CH<sub>2</sub>Cl<sub>2</sub>). Fractions containing product were concentrated, and the residue chromatographed on a silica gel column (15% ethyl acetate/hexanes, flash) to give 924 mg (63% of a pale yellow solid: mp 41°C; IR (KBr) 3053, 2966, 2872, 2819, 1695 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.13 (s, 1H), 7.93 (d, 1H, J=0.9 Hz), 7.77 (d, 1H, J=8.4 Hz), 7.60 (dd, 1H, J=1.2, 8.4 Hz), 5.00 (quintet, 1H, J=7.5 Hz), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.39 (t, 3H, J=7.5 Hz); MS (CI, NH<sub>3</sub>) m/z 243 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.17; H, 7.58; N, 11.79.

## PREPARATION 2

### 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde

[0048]

A. 4-Bromo-2-nitro-1-propyl-benzene. 125 g (628 mmol, 1.0 equiv) 1-bromo-4-propyl-benzene was added in one portion to a 10°C solution of 600 mL conc. H<sub>2</sub>SO<sub>4</sub> and 200 mL H<sub>2</sub>O. With vigorous mechanical stirring, an ambient temperature mixture of 43.2 mL (691 mmol, 1.1 equiv) conc. HNO<sub>3</sub> (69-71%, 16M) in 150 mL conc. H<sub>2</sub>SO<sub>4</sub> and 50 mL H<sub>2</sub>O was added dropwise over 30 minutes. The ice bath was allowed to warm to ambient temperature, and the reaction stirred at room temperature for 68 hours. The reaction mixture was poured into a 4 L beaker, loosely packed full with crushed ice. After stirring 1 hour, the mixture was transferred to a 4 L separatory funnel and

extracted 4 x 800 mL isopropyl ether. The organic extracts were combined, washed 3 x 800 mL H<sub>2</sub>O, 1 x 500 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 150 mL of a yellow liquid, which was purified by silica gel chromatography (2 columns, 3 kg silica gel each, 2% ethyl acetate/hexanes) to afford 63.9 g (42%) of a yellow liquid. The desired regioisomer is the less polar of the two, which are formed in a 1:1 ratio. bp 108°C, 2.0 mm; IR (CHCl<sub>3</sub>) 3031, 2966, 2935, 2875, 1531, 1352 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.01 (d, 1H, J=2.1 Hz), 7.62 (dd, 1H, J=2.1, 8.3 Hz), 7.23 (d, 1H, J=8.3 Hz), 2.81 (m, 2H), 1.67 (m, 2H), 0.98 (t, 3H, J=7.4 Hz); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 13.94, 23.74, 34.43, 119.6, 127.4, 133.3, 135.7, 136.4, 149.8; GCMS (EI) m/z 245/243 (M+.), 147 (base); HRMS calcd for C<sub>9</sub>H<sub>10</sub>NO<sub>2</sub>Br + H: 243.9973. Found: 243.9954.

B. 5-Bromo-2-propyl-phenylamine. 121 g (639 mmol, 3.0 equiv) of stannous chloride (anhydrous) were added in one portion to a room temperature solution of 51.9 g (213 mmol, 1.0 equiv) 4-bromo-2-nitro-1-propyl-benzene in 1200 mL absolute ethanol and 12 mL (6 equiv) H<sub>2</sub>O. After 24 hours at room temperature, most of the ethanol was removed on a rotary evaporator. The residue was poured into a 4 L beaker, 3/4 full with crushed ice and H<sub>2</sub>O. 150 g of NaOH pellets were added portionwise, with stirring, until the pH = 10 and most of the tin hydroxide has dissolved. The mixture was divided in half, and each half extracted 2 x 750 mL ethyl acetate. All four ethyl acetate extracts were combined, washed 1 x 500 mL each 1N NaOH, H<sub>2</sub>O, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave a yellow liquid, which was purified on a 1.2 kg silica gel column (1:12 ethyl acetate/hexanes) to give 41.83 g (92%) of a pale yellow liquid: IR (CHCl<sub>3</sub>) 3490, 3404, 3008, 2962, 2933, 2873, 1620, 1491 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.8-6.9 (m, 3H), 3.90 (br s, 2H), 2.42 (m, 2H), 1.62 (m, 2H), 0.99 (t, 3H, J=7.3 Hz); GCMS (EI) m/z 215/213 (M+.), 186/184 (base); Anal. calcd for C<sub>9</sub>H<sub>12</sub>NBr: C, 50.49; H, 5.65; N, 6.54. Found: C, 50.77; H, 5.70; N, 6.50.

C. 6-Bromo-3-ethyl-1H-indazole. 49.22 g (230 mmol, 1.0 equiv) 5-bromo-2-propyl-phenylamine were placed in a 3 L flask and chilled in an ice bath. A 0°C solution of 57.5 mL (690 mmol, 3.0 equiv) conc. HCl in 165 mL H<sub>2</sub>O was added, and the resulting solid mass which formed was ground up until a fine white suspension resulted. 100 mL more H<sub>2</sub>O were added, then a solution of 15.9 g (230 mmol, 1.0 equiv) sodium nitrite in 75 mL H<sub>2</sub>O was added dropwise over 10 minutes. The ice bath was removed, and the reaction allowed to stir at room temperature for 30 minutes. The reaction mixture was then filtered through a sintered glass funnel, precooled to 0°C. The filtrate was chilled in an ice bath, and with mechanical stirring, a 0°C solution/suspension of 32.8 g (313 mmol, 1.36 equiv) ammonium tetrafluoroborate in 110 mL H<sub>2</sub>O was added dropwise over 10 minutes. The thick white suspension which formed (aryl diazonium tetrafluoroborate salt) was allowed to stir 1.5 hours at 0°C. The mixture was then filtered, and the solid washed 1 x 200 mL 5% aq. NH<sub>4</sub>BF<sub>4</sub> (cooled at 0°C), 1 x 150 mL CH<sub>3</sub>OH (cooled to 0°C), then 1 x 200 mL Et<sub>2</sub>O. Drying at high vacuum, ambient temperature for 1 hour gave 54.47 g (76%) of the diazonium salt, an off-white solid.

1500 mL of ethanol free chloroform were placed in a 3 flask, then 34.16 g (348 mmol, 2.0 equiv) potassium acetate (powdered and dried) and 2.3 g (8.7 mmol, 0.05 equiv) 18-crown-6 were added. After 10 minutes, the diazonium salt was added in one portion, and the reaction mixture allowed to stir at room temperature under nitrogen atmosphere for 18 hours. The mixture was then filtered, the solid washed 2 x with CHCl<sub>3</sub>, and the filtrate concentrated to give 47 g of crude product (brown crystals). Silica gel chromatography (1.2 kg silica gel, ethyl acetate/hexanes gradient 15%, 20%, 40%) gave 21.6 g (55% for second step, 42% overall) of tan crystals: mp 112-114°C; IR (KBr) 3205, 3008, 2969, 2925, 1616, 1340, 1037 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.86 (br s, 1H), 7.61 (d, 1H, J=1.3 Hz), 7.57 (d, 1H, J=8.4 Hz), 7.24 (dd, 1H, J=1.5, 8.6 Hz), 2.99 (q, 2H, J=7.6 Hz), 1.41 (t, 3H, J=7.6 Hz); MS (CI, NH<sub>3</sub>) m/z 227/225 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>9</sub>H<sub>9</sub>N<sub>2</sub>Br: C, 48.02; H, 4.03; N, 12.45. Found: C, 48.08; H, 3.87; N, 12.45.

D. 6-Bromo-1-cyclopentyl-3-ethyl-1H-indazole. 2.46 g (61.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in 0.5 g portions to a 10°C solution of 13.17 g (58.5 mmol, 1.0 equiv) 6-bromo-3-ethyl-1H-indazole in 500 mL anhydrous DMF. The mixture was stirred at ambient temperature for 20 minutes, then a solution of 8.8 mL (81.9 mmol, 1.4 equiv) cyclopentyl bromide in 10 mL anhydrous DMF was added dropwise. After 18 hours, the reaction mixture was poured into 2 L H<sub>2</sub>O and extracted 2 x 1 L ethyl acetate. The organic extracts were combined, washed 2 x 750 mL H<sub>2</sub>O, 1 x 500 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 20.7 g of crude product, which was purified on a silica gel column (1.1 kg silica gel, 3% ethyl acetate/hexanes) to give 10.6 g (62%) of an amber liquid: IR (CHCl<sub>3</sub>) 2972, 2875, 1606, 1501, 1048 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.56 (d, 1H, J=1.3 Hz), 7.52 (d, 1H, J=8.7 Hz), 7.17 (dd, 1H, J=1.5, 8.5 Hz), 4.83 (quintet, 1H, J=7.6 Hz), 2.96 (q, 2H, J=7.6 Hz), 2.15 (m, 4H), 2.0 (m, 2H), 1.65 (m, 2H), 1.36 (t, 3H, J=7.7 Hz); MS (thermospray, NH<sub>4</sub>OAc) m/z 295/293 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>Br: C, 57.35; H, 5.84; N, 9.55. Found: C, 57.48; H, 5.83; N, 9.90.

E. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde. 11.6 mL (28.4 mmol, 1.0 equiv) n-BuLi, 2.45 M in hexanes, were added to a -78°C solution of 8.32 g (28.4 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole in 200 mL anhydrous THF. After 30 min. at -78°C, 8.8 mL (114 mmol, 4.0 equiv) anhydrous DMF were added dropwise, and the reaction mixture was allowed to stir an additional 30 minutes at -78°C. The mixture was warmed to room temperature over 1 hour, then 125 mL 1N HCl were added. After stirring for 10 minutes, most of the THF was

removed on a rotary evaporator. The residue was diluted with 500 mL H<sub>2</sub>O, and extracted 2 x 250 mL ethyl acetate. The organic extracts were combined, washed 1 x 100 mL H<sub>2</sub>O, 1 x 100 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on silica gel column (15% ethyl acetate/hexanes, gravity) to give 4.70 g (68%) of a yellow crystalline solid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) identical to the spectrum of the title compound from Preparation 1.

#### EXAMPLE 1

##### (±)-1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol

[0049]

A. 1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-pyridin-4-yl-methanone. 1.53 mL (3.83 mmol, 1.1 equiv) n-BuLi, 2.5 M in hexanes, were added dropwise to a -78°C solution of 1.02 g (3.48 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole in 10 mL anhydrous THF. After 10 minutes, a room temperature suspension of 417 mg (4.00 mmol, 1.15 equiv) 4-cyanopyridine in 10 mL anhydrous THF was added, and the reaction mixture allowed to stir at -78°C for 45 minutes. The reaction mixture was then allowed to warm to -10°C over 30 minutes. 12 mL of 2N HCl were added, and the reaction stirred at room temperature for 30 minutes. The mixture was poured into 75 mL H<sub>2</sub>O, basified to pH 14 with 1N NaOH, and extracted 2 x 60 mL ethyl acetate. The organic extracts were combined, washed 1 x 25 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 1.19 g of a amber oil, which was purified on a silica gel column (50% ethyl acetate/hexanes) to give 749 mg (67%) of an off-white solid. A small sample was recrystallized from ethyl acetate/hexanes for analytical data: mp 129-131°C; MS (Cl, NH<sub>3</sub>) m/z 320 (M+H<sup>+</sup>, base).

B. (±)-1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol. 952 µL (2.38 mmol, 1.0 equiv) n-BuLi, 2.5 M in hexanes, were added dropwise to a -78°C solution of 231 µL (2.38 mmol, 1.10 equiv) 4-methylpyridine in 10 mL anhydrous THF. After 30 minutes, a room temperature solution of 690 mg 92.16 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-pyridin-4-yl-methanone in 5 mL anhydrous THF was added over 5 minutes. The reaction mixture was allowed to stir 1 hour at -78°C, then 1/2 hour at room temperature. 50 mL H<sub>2</sub>O were added, and the mixture extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 1 x 50 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave a yellow solid, which was purified on a silica gel column (5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give 248 mg (28%) of white crystals: mp 208-211°C; MS (Cl, NH<sub>3</sub>) m/z 413 (M+H<sup>+</sup>, base).

#### EXAMPLE 2

##### 1-Cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole

[0050] 191 mg (0.463 mmol, 1.0 equiv) 1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol, 220 mg (1.16 mmol, 2.5 equiv) p-toluenesulfonic acid and 30 mL anhydrous toluene were placed in a flask fitted with a Dean-Stark trap and heated to reflux under nitrogen atmosphere. After 24 hours, the reaction mixture was cooled to room temperature, diluted with 50 mL ethyl acetate, washed 2 x 15 mL 1N NaOH, 1 x 15 mL H<sub>2</sub>O, 1 x 15 mL brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 180 mg of an off white solid, which was purified on a silica gel column (4% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give 53 mg (29%) of a yellow amorphous solid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.62 (br s, 2H), 8.42 (br s, 2H), 7.63 (dd, 1H, J=0.6, 8.4 Hz), 7.2 (m, 3H), 7.0 (m, 2H), 6.9 (m, 2H), 4.81 (quintet, 1H, J=7.6 Hz), 2.98 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.37 (t, 3H, J=7.6 Hz); MS (Cl, NH<sub>3</sub>) m/z 395 (M+H<sup>+</sup>, base).

#### EXAMPLE 3

##### (±)-1-Cyclopentyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazole hydrochloride

[0051] A mixture of 51 mg (0.129 mmol, 1.0 equiv) 1-cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole and 50 mg 10% Pd/C in 7.5 mL ethanol and 250 µL triethylamine was placed on a Parr® hydrogenation apparatus and shaken under 25 psi H<sub>2</sub> at room temperature for 3.5 hour. The reaction mixture was then filtered through Celite®, and the filtrate concentrated on a rotary evaporator and purified on a silica gel column (5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give 40 mg (78%) of a white solid. This solid was dissolved in 4 mL ether and 202 µL (2.0 equiv) 1N HCl in ether were added. After 15 minutes, the mixture was filtered, and the filtrant dried at high vacuum, room temperature to give 31 mg (66%) of a yellow powder: mp 245-254°C (dec); Anal. calcd for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>•2HCl•3/4H<sub>2</sub>O: C, 64.86; H, 6.60; N, 11.64. Found:

C, 64.75; H, 6.43; N, 11.57.

#### EXAMPLE 4

5 (±)-1-(1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol

[0052]

10 A. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-phenyl-methanol. 3.4 mL (6.08 mmol, 1.0 equiv) phenyl lithium, 1.8 M in cyclohexane/ether, were added dropwise to a -78°C solution of 1.34 g (5.53 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde in 10 mL anhydrous THF. After 30 minutes at -78 ° C, the reaction mixture was allowed to warm to room temperature over 3 hour. 75 mL H<sub>2</sub>O were added, and the mixture extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 1 x 50 mL H<sub>2</sub>O, 1 x 50 ML brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave 1.92 g of a yellow oil, which was purified on a silica gel column (20% ethyl acetate/hexanes) to give 1.49 g (84%) of a pale yellow oil, which crystallized on standing: mp 88-91 °C; MS (Cl, NH<sub>3</sub>) m/z 321 (M+H<sup>+</sup>, base); Anal. calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.21; H, 7.71; N, 8.82.

20 B. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-phenyl-methanone. 72 mg (0.204 mmol, 0.05 equiv) tetrapropylammonium perruthenate (VII) were added to a room temperature suspension of 1.308 g (4.08 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-phenyl-methanol, 717 mg (6.12 mmol, 1.5 equiv) N-methylmorpholine N-oxide and 2.5 g 4A molecular sieves in 25 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub>. After 1 hour, the reaction mixture was filtered through a short column of silica gel (eluted with 100 mL CH<sub>2</sub>Cl<sub>2</sub>, then 75 mL ethyl acetate). Fractions containing product were concentrated, and dried at high vacuum, room temperature to give 1.28 g (98%) of a white crystalline solid: mp 75-77°C; MS (Cl, NH<sub>3</sub>) m/z 319 (M+H<sup>+</sup>, base).

25 C. (±)-1-(1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol. This compound was prepared using the method of example 1, using 1.22 g (3.83 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-phenyl-methanone as starting material, to give 1.06 g (67%) of a white crystalline solid: mp 175-177°C; MS (Cl, NH<sub>3</sub>) m/z 412 (M+H<sup>+</sup>, base).

#### EXAMPLE 5

1-Cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole

35 [0053] 1.00 g (2.43 mmol, 1.0 equiv) (±)-1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol, 578 mg (3.04 mmol, 1.25 equiv) p-toluenesulfonic acid and 25 mL anhydrous toluene were placed in a flask fitted with a Dean-Stark trap and heated to reflux under nitrogen atmosphere. After 7 hours, the reaction mixture was cooled to room temperature and allowed to stir for 72 hours. The reaction mixture was diluted with 200 mL H<sub>2</sub>O and 100 mL 1N NaOH, and extracted 2 x 100 mL ethyl acetate. The organic extracts were combined, washed 1 x 50 mL each H<sub>2</sub>O, brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on a silica gel column (2.5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give 0.92 g (95%) of a white amorphous solid. A small sample was crystallized from ethyl acetate/hexanes to give 27 mg white needles: mp 134-136°C; Anal. calcd for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>: C, 82.41; H, 6.92; N, 10.68; Found: C, 82.31; H, 7.17; N, 10.80.

#### EXAMPLE 6

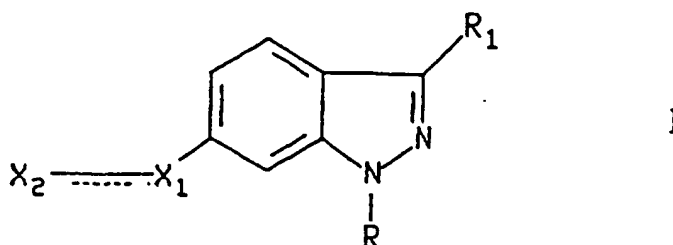
45 (±)-1-Cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazole hydrochloride

[0054] This compound was prepared according to the method of Example 3 using 0.87 g (2.21 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole as starting material, to give 550 mg (59%) pale yellow powder: mp 193-196°C; Anal. calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>•HCl: C, 75.06; H, 7.00; N, 9.73. Found: C, 73.97; H, 7.30; N, 9.77.

#### Claims

55 1. A compound of the formula





15 or a pharmaceutically acceptable salt thereof, wherein:

the broken line indicates a single or double bond;

$X_1$  is  $-CR_2R_3$  where said broken line indicates a single bond or  $-CR_3$  where said broken line indicates a double bond;

$X_2$  is  $-CR_5R_7R_8$  wherein said broken line indicates a single bond or  $-CR_7R_8$  where said broken line indicates a double bond;

$R$  is  $-(CH_2)_m(C_3-C_7 \text{ cycloalkyl})$ , wherein  $m$  is 0 to 2, or  $C_6-C_{10}$  aryl;

$R_1$  is  $C_1-C_7$  alkyl;

$R_2$  is H, hydroxy, halo or  $-OR_9$ ;

$R_3$  is  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , wherein  $n$  is 0 to 3, and  $R_3$  is optionally substituted by 1 to 3  $R_4$  groups;

each  $R_4$  is independently selected from halo, cyano, nitro,  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl or  $-OR_5$ ;

each  $R_5$  is independently H or  $C_1-C_6$  alkyl;

$R_7$  is  $R_3$ ;

$R_8$  is  $R_5$ ; and

$R_9$  is formyl, carbamoyl, thiocarbamyl;  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $(C_1-C_4 \text{ alkoxy}) C_1-C_4$  alkyl, or  $C_1-C_6$  alkanoyl, wherein the alkyl moieties of said  $R_9$  groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, and  $C_1-C_4$  alkoxy.

2. The compound of claim 1 wherein  $R_1$  is ethyl and  $R$  is cyclopentyl, cyclohexyl, or  $C_6-C_{10}$  aryl.

3. The compound of claim 2 wherein  $R_3$  is  $-(CH_2)_n(C_6-C_{10} \text{ aryl})$  or  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , wherein  $n$  is 0 to 3.

4. The compound of claim 3 wherein  $R_3$  is phenyl or pyridin-4-yl.

5. The compound of claim 2 wherein  $R_7$  is  $-(CH_2)_n(5-10 \text{ membered heteroaryl})$ , wherein  $n$  is 0 to 3.

6. The compound of claim 5 wherein  $R_7$  is pyridin-4-yl.

7. The compound of claim 1 wherein the broken line indicates a single bond,  $R_2$  is H,  $R_3$  is phenyl, 3-methyl-phenyl, 4-pyridyl, 2-furyl, 2-thienyl, or 2-methoxy-phenyl,  $R_5$  is H,  $R_8$  is H, and  $R_7$  is 4-pyridyl, 3-methyl-4-imidazolyl, 3,5-dichloro-4-pyridyl, or 4-pyrimidinyl.

8. The compound of claim 1 wherein the broken line indicates a double bond,  $R_3$  is phenyl, 4-methoxy-phenyl, 2-furyl, 2-thienyl, 4-fluoro-phenyl, 4-trifluoromethyl-phenyl or 2-methoxy-phenyl,  $R_8$  is H, and  $R_7$  is 4-pyridyl.

9. The compound of claim 1 wherein said compound is selected from the group consisting of:

1-(cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;

1-cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole;

1-cyclopentyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazole;

1-(cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;

1-(cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole;

1-(cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazole;

and pharmaceutically acceptable salts of the foregoing compounds.

5 10. The compound of claim 1 wherein said compound is selected from the group consisting of:

1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;  
1-cyclohexyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazole;  
1-1-cyclohexyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazole;  
10 1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;  
1-cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazole;  
1-cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazole;

and pharmaceutically acceptable salts of the foregoing compounds.

15 11. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

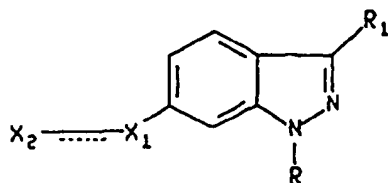
20 12. The use of a therapeutically effective amount of a compound according to claim 1 for the preparation of a medicament for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal.

25 13. A pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoporosis, and other arthritic conditions; sepsis, septic shock, endotoxemic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS),  
30 AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, diabetes insipidus, autoimmune diabetes, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, dermatitis, depression or multi-infarct dementia, comprising a therapeutically effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.

35 14. The use of a therapeutically effective amount of a compound according to claim 1 for the preparation of a medicament for treating or preventing asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoporosis, and other arthritic conditions; sepsis, septic shock, endotoxemic shock, gram negative sepsis,  
40 toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis,  
45 type 1 diabetes mellitus, diabetes insipidus, autoimmune diabetes, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, dermatitis, depression or multi-infarct dementia in a mammal.

## 50 Patentansprüche

### 1. Verbindung der Formel



oder ein pharmazeutisch verträgliches Salz davon,

wobei die unterbrochene Linie eine Einfach- oder Doppelbindung anzeigt;

$X_1$  - $CR_2R_3$  darstellt, wenn die unterbrochene Linie eine Einfachbindung anzeigt oder - $CR_3$  darstellt, wenn die unterbrochene Linie eine Doppelbindung anzeigt;

$X_2$  - $CR_5R_7R_8$  darstellt, wenn die unterbrochene Linie eine Einfachbindung anzeigt oder - $CR_7R_8$  darstellt, wenn die unterbrochene Linie eine Doppelbindung anzeigt;

$R$  -( $CH_2$ ) $_m$ ( $C_3$ - $C_7$ -Cycloalkyl), worin  $m$  0 bis 2 ist, oder  $C_6$ - $C_{10}$ -Aryl darstellt;

$R_1$   $C_1$ - $C_7$ -Alkyl darstellt;

$R_2$  H, Hydroxy, Halogen oder - $OR_9$  darstellt;

$R_3$  -( $CH_2$ ) $_n$ ( $C_6$ - $C_{10}$ )Aryl oder -( $CH_2$ ) $_n$ (5-10-gliedriges Heteroaryl) darstellt, worin  $n$  0 bis 3 ist und  $R_3$  gegebenenfalls mit 1 bis 3 Gruppen  $R_4$  substituiert ist;

jeder Rest  $R_4$  unabhängig voneinander aus Halogen, Cyano, Nitro,  $C_1$ - $C_6$ -Alkyl,  $C_2$ - $C_6$ -Alkenyl oder - $OR_5$  ausgewählt ist;

jeder Rest  $R_5$  unabhängig voneinander H oder  $C_1$ - $C_6$ -Alkyl darstellt;

$R_7$   $R_3$  darstellt;

$R_8$   $R_5$  darstellt; und

$R_9$  Formyl, Carbamoyl, Thiocarbamyl;  $C_1$ - $C_6$ -Alkyl,  $C_2$ - $C_6$ -Alkenyl, ( $C_1$ - $C_4$ -Alkoxy)- $C_1$ - $C_4$ -alkyl oder  $C_1$ - $C_6$ -Alkanoyl darstellt, worin die Alkyleinheiten der Gruppen  $R_9$  gegebenenfalls mit 1 bis 3 Substituenten, unabhängig voneinander ausgewählt aus Halogen, Hydroxy und  $C_1$ - $C_4$ -Alkoxy, substituiert sind.

2. Verbindung nach Anspruch 1, worin  $R_1$  Ethyl darstellt und  $R$  Cyclopentyl, Cyclohexyl oder  $C_6$ - $C_{10}$ -Aryl darstellt.

3. Verbindung nach Anspruch 2, worin  $R_3$  -( $CH_2$ ) $_n$ ( $C_6$ - $C_{10}$ -Aryl) oder -( $CH_2$ ) $_n$ (5-10-gliedriges Heteroaryl) darstellt, worin  $n$  0 bis 3 ist.

4. Verbindung nach Anspruch 3, worin  $R_3$  Phenyl oder Pyridin-4-yl darstellt.

5. Verbindung nach Anspruch 2, worin  $R_7$  -( $CH_2$ ) $_n$ (5-10-gliedriges Heteroaryl) darstellt, worin  $n$  0 bis 3 ist.

6. Verbindung nach Anspruch 5, worin  $R_7$  Pyridin-4-yl darstellt.

7. Verbindung nach Anspruch 1, worin die unterbrochene Linie eine Einfachbindung ausweist,  $R_2$  H darstellt,  $R_3$  Phenyl, 3-Methylphenyl, 4-Pyridyl, 2-Furyl, 2-Thienyl oder 2-Methoxyphenyl darstellt,  $R_5$  H darstellt,  $R_8$  H darstellt und  $R_7$  4-Pyridyl, 3-Methyl-4-imidazolyl, 3,5-Dichlor-4-pyridyl oder 4-Pyrimidinyl darstellt.

8. Verbindung nach Anspruch 1, worin die unterbrochene Linie eine Doppelbindung ausweist,  $R_3$  Phenyl, 4-Methoxyphenyl, 2-Furyl, 2-Thienyl, 4-Fluorphenyl, 4-Trifluormethylphenyl oder 2-Methoxyphenyl darstellt,  $R_8$  H darstellt und  $R_7$  4-Pyridyl darstellt.

9. Verbindung nach Anspruch 1, worin die Verbindung ausgewählt ist aus der Gruppe, bestehend aus:

1-(-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;

1-Cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazol;

1-Cyclopentyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazol;

1-(-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;

1-(-Cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazol;

1-(-Cyclopentyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazol;

und pharmazeutisch verträgliche Salze der vorangehenden Verbindungen.

10. Verbindung nach Anspruch 1, worin die Verbindung ausgewählt ist aus der Gruppe, bestehend aus:

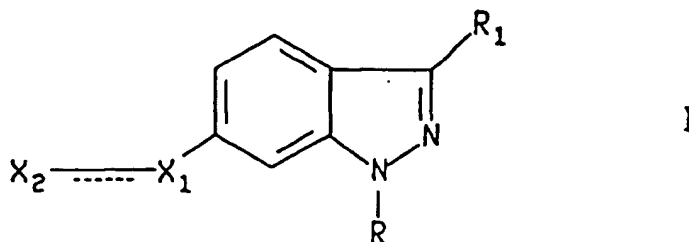
- 5 1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-ethanol;
- 1-Cyclohexyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-ethyl-1H-indazol;
- 1-1-Cyclohexyl-6-(1,2-di-pyridin-4-yl-ethyl)-3-ethyl-1H-indazol;
- 1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-1-phenyl-2-pyridin-4-yl-ethanol;
- 1-Cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-vinyl)-1H-indazol;
- 10 1-Cyclohexyl-3-ethyl-6-(1-phenyl-2-pyridin-4-yl-ethyl)-1H-indazol;

und die pharmazeutisch verträglichen Salze der vorangehenden Verbindungen.

- 11. Pharmazeutische Zusammensetzung zur Inhibierung von Phosphodiesterase-(PDE)-Typ IV oder der Erzeugung von Tumornekrosefaktor (TNF), umfassend eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 und einen pharmazeutisch verträglichen Träger.
- 12. Verwendung einer therapeutisch wirksamen Menge einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels zur Inhibierung von Phosphodiesterase-(PDE)-Typ IV oder der Erzeugung von Tumornekrosefaktor (TNF) in einem Säuger.
- 13. Pharmazeutische Zusammensetzung zur Vorbeugung oder Behandlung von Asthma, Gelenkentzündung, rheumatischer Arthritis, Gichtarthritis, rheumatischer Spondylitis, Osteoporose und anderen arthritischen Zuständen; Sepsis, septischem Schock, endotoxischem Schock, gram-negativer Sepsis, toxischem Schocksyndrom, akutem respiratorischem Insuffizienzsyndrom, cerebraler Malaria, chronischer Lungenentzündung, Silicose, pulmonaler Sarkoidose, Knochenresorptionserkrankung, Wiederdurchblutungsstörung, Transplantat gegen Wirtsreaktion, Alлотransplantatabstoßungen, Fieber und Muskelschmerz aufgrund von Infektion, wie Influenza, Kachexie sekundär zur Infektion oder Bösartigkeit, Kachexie sekundär zum erworbenen Human-Immunmangelsyndrom (AIDS), AIDS, HIV, ARC (AIDS-bedingter Komplex), Keloidbildung, Narbengewebsbildung, Crohn'scher Krankheit, ulcerativer Colitis, Pyrese, multipler Sklerose, Diabetes mellitus Typ 1, Diabetes insipidus, Autoimmundiabetes, systemischem Lupus erythematosus, Bronchitis, chronischer obstruktiver Lungenerkrankung, Psoriasis, Bechet's-Erkrankung, anaphylaktischem hämorrhagischem renalem Syndrom, chronischer Glomerulonephritis, entzündlicher Darmerkrankung, Leukämie, allergischem Schnupfen, Dermatitis, Depression oder Multi-Infarkt-Demenz, umfassend eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1, zusammen mit einem pharmazeutisch verträglichen Träger.
- 14. Verwendung einer therapeutisch wirksamen Menge einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels zur Behandlung oder Verhinderung von Asthma, Gelenkentzündung, rheumatischer Arthritis, Gichtarthritis, rheumatischer Spondylitis, Osteoporose und anderen arthritischen Zuständen; Sepsis, septischem Schock, endotoxischem Schock, gram-negativer Sepsis, toxischem Schocksyndrom, akutem respiratorischem Insuffizienzsyndrom, cerebraler Malaria, chronischer Lungenentzündung, Silicose, pulmonaler Sarkoidose, Knochenresorptionserkrankung, Wiederdurchblutungsstörung, Transplantat gegen Wirtsreaktion, Alлотransplantatabstoßungen, Fieber und Muskelschmerz aufgrund von Infektion, wie Influenza, Kachexie sekundär zur Infektion oder Bösartigkeit, Kachexie sekundär zum erworbenen Human-Immunmangelsyndrom (AIDS), AIDS, HIV, ARC (AIDS-bedingter Komplex), Keloidbildung, Narbengewebsbildung, Crohn'scher Krankheit, ulcerativer Colitis, Pyrese, multipler Sklerose, Diabetes mellitus Typ 1, Diabetes insipidus, Autoimmundiabetes, systemischem Lupus erythematosus, Bronchitis, chronischer obstruktiver Lungenerkrankung, Psoriasis, Bechet's-Erkrankung, anaphylaktischem hämorrhagischem renalem Syndrom, chronischer Glomerulonephritis, entzündlicher Darmerkrankung, Leukämie, allergischem Schnupfen, Dermatitis, Depression oder Multi-Infarkt-Demenz, bei einem Säuger.

## Revendications

1. Composé répondant à la formule



ou un de ses sels pharmaceutiquement acceptable, dans lequel :

la ligne en traits interrompus indique une liaison simple ou double ;

$X_1$  est un radical  $-CR_2R_3$  lorsque cette ligne en traits interrompus indique une liaison simple ou un radical  $-CR_3$  lorsque cette ligne en traits interrompus indique une liaison double ;

$X_2$  est un radical  $-CR_5R_7R_8$  lorsque cette ligne en traits interrompus indique une liaison simple ou un radical  $-CR_7R_8$  lorsque cette ligne en traits interrompus indique une liaison double ;

R est un radical  $-(CH_2)_m$  (cycloalkyle en  $C_6$  à  $C_7$ ), dans lequel m est un nombre de 0 à 2, ou un groupe aryle en  $C_6$  à  $C_{10}$  ;

$R_1$  est un groupe alkyle en  $C_1$  à  $C_7$  ;

$R_2$  est H, un groupe hydroxy, un groupe halogéno ou un groupe  $-OR_9$  ;

$R_3$  est un groupe  $-(CH_2)_n$  (aryle en  $C_6$  à  $C_{10}$ ) ou un groupe  $-(CH_2)_n$  (hétéroaryle à 5 à 10 maillons), dans lequel n est un nombre de 0 à 3, et  $R_3$  est substitué si on le désire par 1 à 3 groupes  $R_4$  ;

chacun des radicaux  $R_4$  est choisi indépendamment parmi un groupe halogéno, cyano, nitro, alkyle en  $C_1$  à  $C_6$ , alcényle en  $C_2$  à  $C_6$  ou  $-OR_5$  ;

chacun des radicaux  $R_5$  est indépendamment H ou un groupe alkyle en  $C_1$  à  $C_6$  ;

$R_7$  est  $R_3$  ;

$R_8$  est  $R_5$  ; et

$R_9$  est un groupe formyle, carbamoyle, thiocarbamyle ; alkyle en  $C_1$  à  $C_6$ , alcényle en  $C_2$  à  $C_6$ , (alkoxy en  $C_1$  à  $C_4$ ) alkyle en  $C_1$  à  $C_4$ , ou alcanoyle en  $C_1$  à  $C_6$ , dans lequel les parties alkyle de ces groupes  $R_9$  sont substituées si on le désire par 1 à 3 substituants choisis indépendamment parmi les groupes halogéno, hydroxy et alkoxy en  $C_1$  à  $C_4$ .

2. Composé selon la revendication 1, dans lequel  $R_1$  est un groupe éthyle et R est un groupe cyclopentyle, cyclohexyle ou aryle en  $C_6$  à  $C_{10}$ .
3. Composé selon la revendication 2, dans lequel  $R_3$  est un groupe  $-(CH_2)_n$  (aryle en  $C_6$  à  $C_{10}$ ) ou un groupe  $-(CH_2)_n$  (hétéroaryle à 5 à 10 maillons), dans lequel n est un nombre de 0 à 3.
4. Composé selon la revendication 3, dans lequel  $R_3$  est un groupe phényle ou pyridin-4-yle.
5. Composé selon la revendication 2, dans lequel  $R_7$  est un groupe  $-(CH_2)_n$  (hétéroaryle à 5 à 10 maillons), dans lequel n est un nombre de 0 à 3.
6. Composé selon la revendication 5, dans lequel  $R_7$  est un groupe pyridin-4-yle.
7. Composé selon la revendication 1, dans lequel la ligne en traits interrompus indique une liaison simple,  $R_2$  est H,  $R_3$  est un groupe phényle, 3-méthyl-phényle, 4-pyridyle, 2-furyle, 2-thiényle ou 2-méthoxy-phényle,  $R_5$  est H,  $R_8$  est H, et  $R_7$  est un groupe 4-pyridyle, 3-méthyl-4-imidazolyle, 3,5-dichloro-4-pyridyle ou 4-pyrimidinyle.
8. Composé selon la revendication 1, dans lequel la ligne en traits interrompus indique une liaison double,  $R_3$  est un groupe phényle, 4-méthoxy-phényle, 2-furyle, 2-thiényle, 4-fluoro-phényle, 4-trifluorométhyl-phényle ou 2-méthoxy-phényle,  $R_8$  est H, et  $R_7$  est un groupe 4-pyridyle.
9. Composé selon la revendication 1, dans lequel ce composé est choisi dans le groupe constitué :

du 1-(cyclopentyl-3-éthyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-éthanol ;

du 1-cyclopentyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-éthyl-1H-indazole ;  
 du 1-cyclopentyl-6-(1,2-di-pyridin-4-yl-éthyl)-3-éthyl-1H-indazole ;  
 du 1-(1-cyclopentyl-3-éthyl-1H-indazol-6-yl)-1-phényl-2-pyridin-4-yl-éthanol ;  
 du 1-(1-cyclopentyl-3-éthyl-6-(1-phényl-2-pyridin-4-yl-vinyl)-1H-indazole ;  
 du 1-(1-cyclopentyl-3-éthyl-6-(1-phényl-2-pyridin-4-yl-éthyl)-1H-indazole ;

et des sels pharmaceutiquement acceptables des composés qui précèdent.

10. Composé selon la revendication 1, dans lequel ce composé est choisi dans le groupe constitué :

du 1-(1-cyclohexyl-3-éthyl-1H-indazol-6-yl)-1,2-di-pyridin-4-yl-éthanol ;  
 du 1-cyclohexyl-6-(1,2-di-pyridin-4-yl-vinyl)-3-éthyl-1H-indazole ;  
 du 1-1-cyclohexyl-6-(1,2-di-pyridin-4-yl-éthyl)-3-éthyl-1H-indazole ;  
 du 1-(1-cyclohexyl-3-éthyl-1H-indazol-6-yl)-1-phényl-2-pyridin-4-yl-éthanol ;  
 du 1-cyclohexyl-3-éthyl-6-(1-phényl-2-pyridin-4-yl-vinyl)-1H-indazole ;  
 du 1-cyclohexyl-3-éthyl-6-(1-phényl-2-pyridin-4-yl-éthyl)-1H-indazole ;

et des sels pharmaceutiquement acceptables des composés qui précèdent.

11. Composition pharmaceutique pour l'inhibition de la phosphodiesterase (PDE) type IV ou la production du facteur de nécrose des tumeurs (TNF) comprenant une quantité thérapeutiquement efficace d'un composé selon la revendication 1 et d'un support pharmaceutiquement acceptable.

12. Utilisation d'une quantité thérapeutiquement efficace d'un composé selon la revendication 1 pour la préparation d'un médicament pour l'inhibition de la phosphodiesterase (PDE) type IV ou la production du facteur de nécrose des tumeurs (TNF) chez un mammifère.

13. Composition pharmaceutique pour la prévention ou le traitement de l'asthme, de l'inflammation articulaire, de l'arthrite rhumatoïde, de l'arthrite goutteuse, de la spondylite rhumatoïde, de l'ostéoporose et d'autres états arthritiques, de la septicémie, du choc septique, du choc endotoxique, de la septicémie Gram négative, du syndrome de choc toxique, du syndrome de détresse respiratoire aiguë, de l'accès cérébral, de l'inflammation pulmonaire chronique, de la silicose, de la sarcoïdose pulmonaire, des maladies de la résorption osseuse, des plaies de reperfusion, de la réaction de la greffe sur l'hôte, des rejets d'allogreffes, de la fièvre et des myalgies dues à une infection, telles que l'influenza, la cachexie secondaire à l'infection ou à une affection maligne, la cachexie secondaire due au syndrome d'immunodéficience acquise humaine (SIDA), SIDA, HIV, ARC (complexe lié au SIDA), formation chéloïdienne, formation de tissu cicatriciel, maladie de Crohn, colite ulcéreuse, pyrése, sclérose multiple, diabète sucré du type 1, diabète insipide, diabète auto-immun, lupus érythémateux systémique, bronchite, maladie obstructive chronique des voies respiratoires, psoriasis, maladie de Bechet, purpura anaphylactoïde, glomérulonéphrite chronique, inflammation des intestins, leucémie, rhinite allergique, dermatite, dépression ou démence à accès multiples, comprenant une quantité thérapeutiquement efficace d'un composé selon la revendication 1 avec un support pharmaceutiquement acceptable.

14. Utilisation d'une quantité thérapeutiquement efficace d'un composé selon la revendication 1 pour la préparation d'un médicament pour le traitement ou la prévention de l'asthme, de l'inflammation articulaire, de l'arthrite rhumatoïde, de l'arthrite goutteuse, de la spondylite rhumatoïde, de l'ostéoporose et d'autres états arthritiques, de la septicémie, du choc septique, du choc endotoxique, de la septicémie Gram négative, du syndrome de choc toxique, du syndrome de détresse respiratoire aiguë, de l'accès cérébral, de l'inflammation pulmonaire chronique, de la silicose, de la sarcoïdose pulmonaire, des maladies de la résorption osseuse, des plaies de reperfusion, de la réaction de la greffe sur l'hôte, des rejets d'allogreffes, de la fièvre et des myalgies dues à une infection, telles que l'influenza, la cachexie secondaire à l'infection ou à une affection maligne, la cachexie secondaire due au syndrome d'immunodéficience acquise humaine (SIDA), SIDA, HIV, ARC (complexe lié au SIDA), formation chéloïdienne, formation de tissu cicatriciel, maladie de Crohn, colite ulcéreuse, pyrése, sclérose multiple, diabète sucré du type 1, diabète insipide, diabète auto-immun, lupus érythémateux systémique, bronchite, maladie obstructive chronique des voies respiratoires, psoriasis, maladie de Bechet, purpura anaphylactoïde, glomérulonéphrite chronique, inflammation des intestins, leucémie, rhinite allergique, dermatite, dépression ou démence à accès multiples chez un mammifère.